REMARKS

Applicants have amended claim 9 and added new claims 19-22. Claims 1-8, 10-13 and 15 have been canceled without prejudice or disclaimer. Upon entry of this amendment, claims 9, 14 and 16-22 will be under examination.

Support for the amended claim 9 can be found in the specification, for example, Figure 1, page 14, lines 20-26, and page 19, Example 1. New claims 19-21 are supported by the specification at page 1, lines 35-36. New claim 22 is supported by the specification at page 7, lines 26-27. No new matter has been added.

The office action is discussed below.

Anticipation Rejection:

On pages 2-3 of the office action, the examiner has rejected the claims and alleged as being anticipated by both Ritterhaus *et al.,* U.S. Patent No. 6,193,979 and Smith *et al.,* U.S. Patent No. 6,713,606. Applicants respectfully disagree with the examiner and traverse the rejection.

Applicants note that in order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim term is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v.*

Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (Rev. 2, May 2004). Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (Rev. 2, May 2004). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111(Rev. 2, May 2004).

Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964). Applicants review below the references with these concepts in mind.

The Ritterhaus *et al.* disclosure relates to a composition comprising complement proteins related to the complement receptor type 1 (CR1) and preferably in combination with the Lewis X antigen or the sialyl Lewis X antigen (see column 1, lines 16-25). The Smith *et al.* disclosure relates to soluble derivatives of soluble peptides that can be used according to the invention. The present claims, however, are not solely directed to such composition or

derivatives, but rather inventive methods of use for soluble derivatives. Such claims are specifically permitted under 35 USC §§ 100(b), 101.

The cited references do not teach or suggest methods for preparing an organ by perfusion prior to transplantation or storage of the organ by providing an ischemic reperfusion injury prevention preparation for perfusion of an organ prior to transplantation or storage of the organ. Because the references do not concern such a method, thus, the references cannot anticipate the claims, as explained in greater detail below.

On page 2 of the office action, the examiner states that Ritterhaus *et al.* teach compositions that comprise complement-related protein (CR1) with Lewis X antigen or the sialyl Lewis X antigen, a carbohydrate moiety, thus anticipates the claimed invention. In response, applicants provide the following in order to assist the examiner in distinguishing the claimed invention from the cited art:

Ritterhaus *et al.* refer to forms of soluble CR1 (sCR1), wherein the polypeptide chain contains modified glycoforms (including Le^x and sialyl Le^x) (see for example, col. 9, lines 58-66), which are not intrinsically membrane-interactive. The compositions of Ritterhaus *et al.* mediate binding to membranes only if a protein, for which these glycoform modifications are ligands, is expressed in a membrane-bound form on cells. The Ritterhaus *et al.* subject matter is based on such proteins (such as E-selectin), which can be up-regulated

in certain tissues under certain conditions. However, Ritterhaus *et al.* provide no evidence that selectins are up-regulated within a stored organ or that such upregulation is sufficient to bind enough sCR1 (sialyl Le^x) to protect the organ against complement attack. In fact, one skilled in the art would have regarded Ritterhaus *et al.* as being unable to provide such protection because Ritterhaus *et al.* would require the sCR1 derivative to be retained within the organ following flushing with excess preservation fluid and restoration of blood flow. See, for example, Takada *et al., J. Clin. Investigation* 99: 2682-90 (1997) (copy previously submitted). Takada *et al.* showed that when rat kidneys are subjected to warm or cold ischemia, the up-regulation of E-selectin is low at 3-hour post-reperfusion and does not reach the peak until after 6 hours of reperfusion. Not a single construct disclosed in the Rittershaus *et al.*, if delivered by pre-transplantation perfusion, would be retained in an ischemic human kidney long enough to exert any effect on complement activation because it would be washed out of the organ before its cellular target is expressed.

In contrast, the claimed methodology employs soluble derivatives that can bind to any cell membrane, and are not dependent on the presence of an up-regulated protein for binding. This allows delivery and retention of very high levels of a complement regulatory molecule to an organ. Applicant has previously provided a recent publication to show that the retention of bulk APT

"070" (see the right column of Figure 1) has been achieved with human kidneys. See, Pratt *et al.* J *Amer Pathol.* 163: 1457-63 (2003).

Applicants also note that Rittershaus *et al.* disclosed a CR1 fragment, which was modified by glycoform manipulation. Such modification is not possible for SEQ ID NO:1 because it lacks a single N-linked glycosylation site from which a sialyl Le^x structure could be attached. Thus, even if the composition of Ritterhaus *et al.* were to be retained in ischemic organs, they could not be derived from the region of CR1 utilized in the instant invention.

On page 3 of the office action, the examiner rejected claims 9, 14, 15, 17, and 18 as being anticipated by Smith *et al.* (US Patent No. 6,713,606). The examiner alleged that the CR1 of Smith *et al.* "would comprise SCRs (claim 15) and membrane binding elements consistent with claim 17 [and] derivatized with an myristoyl group ([ ] claim 18)." In response, in order to assist the examiner in distinguishing the claimed invention and the cited art, applicants submit the following:

Smith *et al.* disclose complement regulators modified with combinations of membrane-binding elements that can be administered to patients. The examiner has not addressed the unexpected results obtained by using the recited soluble derivative, which encompasses APT "070". Applicants previously submited a recent publication to show the unexpected finding of the effect of APT "070" on

the cellular immune system (see Pratt *et al.* 2003, for example, Figure 6). The results show that pre-treating kidneys with APT070 by perfusion led to a reduction of staining for CD3 and CD45 antigens in transplanted kidneys, which is an indication of reduced infiltration by T-cells (see Pratt *et al.*, Fig 6f). This means that treatment with APT070 reduced the immunogenicity of the grafted organ - a very important influence on the subsequent fate of the graft. Pratt *et al.* concluded that "the transplanted kidney may be a particularly important organ for therapeutic complement regulation." This conclusion emerged from studies of animals deficient in decay-accelerating factor (DAF, CD55). CR1 also has this activity but it is localized specifically in certain regions of the multi-sCR structure of CR1. The fragment of CR1 used in APT070 possesses strong DAF-like activity but other recombinant fragments of CR1 do not. Thus, the T-cell immunomodulatory effects of APT070 are due to a combination of a type of regulatory activity found within this specific CR1 fragment and a membrane-binding element array which together permit the agent to function like exogenous DAF.

The above-described immunomodulatory mechanism could not have been predicted from the membrane-localizing concept disclosed in Smith *et al.*, nor by the mechanisms of cellular adherence exploited by Ritterhaus *et al.* Its significance lies in the combination of known anti-reperfusion injury mechanisms

and immunomodulatory function which makes the recited soluble derivatives, including APT070, particularly well suited for application in transplantation.

Withdrawal of the anticipation rejection in view of the foregoing remarks is requested.

Obviousness Rejection:

On pages 3-4 of the office action, the examiner rejected claims 9 and 18 under 35 USC § 103(a) and alleged as being unpatentable over Ritterhaus *et al.* in view of Smith *et al.* The examiner states that sCR1 peptides of Ritterhaus *et al.* would inherently comprise the sCRs, the SEQ ID NO. 1, and the membrane binding elements of the instant invention. The examiner further speculates that a skilled artisan would be able to combine the sCR1 peptides of Ritterhaus *et al.* and the myristoyl group of Smith *et al.* to arrive at the composition used in the claimed methods. Applicants respectfully disagree with the examiner and refer to arguments above, made in response to the alleged anticipation rejection.

Applicants also point out that Smith *et al.* do not disclose the method for preparing an organ using the recited soluble derivatives, including the APT "070" composition, and thus does not rectify the deficiencies of Ritterhaus *et al.*, as described above. Therefore, the combination of Smith *et al.* and Ritterhaus *et al.*

does not make the claimed invention obvious. Thus, withdrawal of the obviousness rejection is requested.

REQUEST

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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